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Effects of Methyl and Methoxy Derivatives of Phencyclidine on Food and Water Intake

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Abstract: The present study examined whether administration of PCP and its methyl and methoxy derivatives affect food and water intake under deprivation. Animals were deprived for 24 h before tested for food and water intake. The PCP and its derivatives were injected intraperitoneally and treated groups measured 1-12 h for food and 30-180 min for water intake post-injection. The results showed that, both of derivatives, can increase food and water intake in comparison to the PCP and saline groups. Methyl and methoxy derivatives of phencyclidine may affect central systems that are involved in feeding behavior.

Key words: Phencyclidine, derivatives, food intake, water intake, methyl, methoxy

INTRODUCTION

Phencyclidine (1-(1-phenylcyclohexyl) piperidine, CAS 956-90-1, PCP, I (Fig. 1) and its derivatives display analgesic (Ahmadi *et al*., 2005; Bowdle *et al*., 1998), stimulant (Javitt *et al*., 1997; Witkin, 1995), anticonvulsant (Geller *et al*., 1981; Thurkauf *et al*., 1990) and behavioral effects (Balster and Chait, 1976; Chen *et al*., 1959) because of specific binding sites in the brain (Chen *et al*., 1959).

The PCP binds to the N-Methyl-D-Asparate (NMDA) receptor complex and blocks NMDA-mediated gating of the calcium channel conductance (Kapur and Seeman, 2002; Olney *et al*., 1991). These classified and have many behavioral effects in common with other phencyclidine-like drugs, including anaesthetics, antinociceptives, psychotomimetics, anticonvulsants, neuroprotectives and amnesic drugs concern to non-competitive, open channel blockers of the NMDA receptor (Honey *et al*., 1985). However different receptors in the central nervous system are involved in the modulation of behavioral effect of PCP and its analogues. Earlier studies showed the important role of nicotine and nicotinic acetylcholine receptors on feeding behaviors of animals and PCP analogues have been shown the inhibiting nicotinic acetylcholine receptor channels (nAChR) in rats (Carroll and Carmona, 1991; Fryer and Lukas, 1999; Etuk *et al*., 2006). The recent studies also showed that NMDA receptor antagonists PCP have direct effects on serotonin (5-HT) receptors and systemic PCP treatment elevates brain extracellular 5-HT level by interaction with 5-HT reuptake site. Serotonin has been extensively implicated in an array of behavioral and physiological functions including the control of ingestive behaviors (Noda *et al*., 2000; Yamada *et al*., 1999; Iranparvar *et al*., 2006).

Therefore, it seems that all of the NMDA glutamatergic system, nicotinic acetylcholine receptors and serotonin (5-HT) receptors have very important role on modulation of ingestive behavior (Clarke and Kumar, 1984; Guan *et al*., 2004; Saadoun and Cabrera, 2002; Zeni *et al*., 2000).

In this study, two methyl and methoxy hydroxyl derivatives of phencyclidine (45) [(1-[1-(4-methylphenyl) (cyclohexyl)] 4-piperidinol, II), (1-[1-(4-methoxyphenyl) (cyclohexyl)] 4-piperidinol, III)] were tested for food and water intake on rats and compared to PCP and vehicle.

MATERIAL AND METHODS

Preparations of derivatives: Cyclohexanone, Piperidine, Bromo benzene, Magnesium turning, Diethyl ether, 4-bromo toluene, 4-bromo anisole, 4-piperidinol and all other chemicals, were purchase from Merck Chemical Co., (Darmstadt, Germany). Melting points (uncorrected) were determined using a digital Electrothermal melting point apparatus (model 9100, Electrothermal Engineering Ltd., Essex, UK). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz (model AMX, Karlsruhe, Germany) spectrometer (internal reference: TMS). IR spectra were recorded on a Thermo Nicolet FT-IR (model Nexus-870, Nicolet Instrument Corp, Madison, Wisconsin, USA) spectrometer. Mass spectra were recorded on an Agilent Technologies 5973, Mass Selective Detector (MSD) spectrometer (Wilmigton, USA). Column chromatographic

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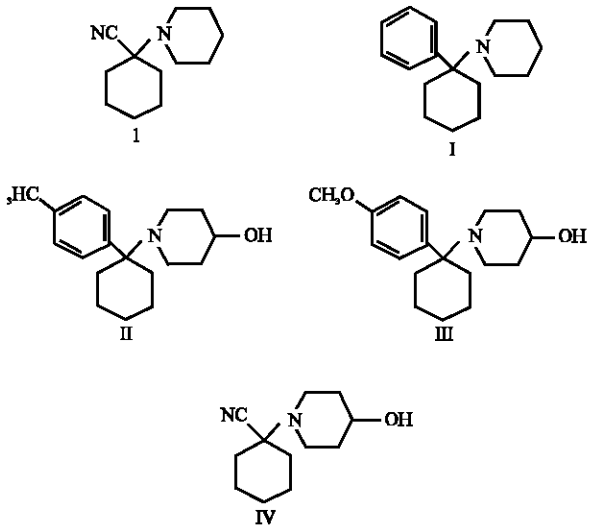

Fig. 1: Structure formulas of PCP (I), PCP-CH_3-OH (II) (methyl), PCP-OCH_3-OH (III) (methoxy) and Carbonitrile intermediates 1 and IV

separations were performed over Acros silica gel (No. 7631-86-9 particle size 35-70 μm, Geel, Belgium). Adult male Wistar rats (Pasteur's Institute, Tehran, Iran), weighing 220-260 g were used for pharmacological testing.

4-hydroxypiperidinocyclohexylcarbonitrile IV: This compound was prepared in an organic solvent to a published method (Effenberger *et al*., 2002) from 4-piperidinol, cyclohexanone and KCN (Fig. 1).

(1-(1-phenylcyclohexyl) piperidine I (PCP): This compound was prepared according to a published method (Shulgin and MacLean 1976) from 1-piperidinocyclohexanecarbonitrile (1) and phenyl magnesium bromide. The hydrochloride salt of I was prepared using 2-propanol and HCl and was recrystallized from 2-propanol (Shulgin and MacLean, 1976) (Fig. 1).

1-(4-methylphenyl) (cyclohexyl) 4-piperidinol, II) (Methyl derivatives): This compound was prepared from nitrile compound (IV) and *p*-tolyl magnesium bromide (Grignard reagent) according to a published method (Ahmadi *et al*., 2009).

The hydrochloride salt of II was prepared using 2-propanol and HCl and was recrystallized from 2-propanol (Ahmadi *et al*., 2009) (Fig. 1).

1-(4-methoxyphenyl) (cyclohexyl) 4-piperidinol, III) (Methoxy derivatives): This compound was prepared from nitrile compound (IV) and *p*-amisol magnesium bromide (Grignard reagent) according to a published method (Ahmadi *et al*., 2009).

The hydrochloride salt of III was prepared using 2-propanol and HCl and was recrystallized from 2-propanol (Ahmadi *et al*., 2009) (Fig. 1).

Behavioral methods: Adult male Wistar rats (Pasteur's Institute), weighing 250±5 g were housed in individual polypropylene cages under controlled temperature (25°C) and light (12 h: 7 a.m. to 7 p.m.)/dark (12 h) cycle with ad libitum access to food (standard laboratory rat chow, Pars company, Tehran, Iran) and water. The experimental procedures adhered to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH) and those of the Research Council of Biology Department of Karaj Azad University (Karaj).

Drug injections: At the beginning of the experiment, the animals were intraperitoneally injected with saline (vehicle) (0.2 mL) and Phencyclidine (PCP) PCP-CH_3-OH (II), PCP-OCH_3-OH (III) hydrochloride at the doses of 1, 5 and 10 mg kg^{-1} that were dissolved in saline.

The cumulative food and water intake were measured (1-12 h for food and 30-180 min for water) after injection of the solutions.

Food intake study: In this experiment, the four groups of animals after 1 week of habituation to their new housing conditions, deprived of food for 24 h (rats were fasted in separate cages with free access to water), after fasting period divided to equal groups and intraperitoneally (IP) injected with drugs (PCP, methyl and methoxy derivatives) (1, 5 and 10 mg kg^{-1}, solved in 0.2 mL saline). Control group was received equivalent volume of saline. Immediately after injection each rat was returned to its cage and a weighed hopper of food were placed in the cage. The quantities of cumulative food (standard laboratory rat chow) consumed were measured (1-12 h) after injection of the solutions (Andersson *et al*., 2004; Zeni *et al*., 2000; Zorrilla *et al*., 2005).

Water intake study: Rats had free access to water and food and were put in the separate metabolic cages at least 7 days before the experiments began. The amount of water ingested in the various experiments was measured with 0.1 mL graduated glass burettes adapted with a metal drinking spout. Intake was induced by water deprivation during the 24 h that preceded the experiment. Groups of animals, IP injected with PCP, Methyl and Methoxy derivatives (1, 5 and 10 mg kg^{-1}; 0.2 mL saline). Control group was received equivalent volume of saline. Immediately after injection each rat was returned to its cage and we measured the cumulative water intake 30-180 min after injection of the solutions. The numbers of rats were six in each group (Aceto *et al*., 1987; Xu and Johnson, 1998; Zorrilla *et al*., 2005).

Statistical methods: Since, data displayed normality of distribution and homogeneity of variance, one-way ANOVA and Tukey Post hoc test (SPSS software) were used for comparison between the effects of different doses of extract with control. The Microsoft Excel software was used for drawing graphs. The $p<0.05$ level was considered to represent significant difference. The study was carried out in 2009.

RESULTS

Phencyclidine (PCP), 1-[1-(4-methylphenyl) (cyclohexyl) 4-piperidinol (Methyl derivatives) and 1-[1-(4-methoxyphenyl) (cyclohexyl) 4-piperidinol (Methoxy derivatives) were synthesized by reaction of substituted Grignard reagents and carbonitrile compounds (45). This compounds (Methyl derivatives, Methoxy derivatives) have stronger hydrophilic and polarity (a hydroxyl group on the piperidine ring) and the high electron donating, distribution and dipole moments (a methyl or methoxy group on the aromatic ring) properties. Known procedures were applied for the synthesis of all compounds I-IV with the appropriate modifications described previously (Effenberger *et al.*, 2002; Maddox *et al.*, 1965; Shebley *et al.*, 2006).

Animal behavioral observation showed no mortality, morbidity, irritability and other side effects due to drugs administration. However, comparison of the motor coordination index (was measured by Rota-rod apparatus, Harvard, UK) indicated no significant differences between control and treatment rats.

The results showed that IP injection of two derivatives of phencyclidine Methyl and Methoxy derivatives (1, 5 and 10 mg kg^{-1}) increase food consumption in comparison to the saline group in the food deprived rats (Fig. 2, 3). However, food deprived animal showed no changes in food intake after any of the PCP treatments (Fig. 4).

Methyl and Methoxy derivatives (1, 5 and 10 mg kg^{-1}) injected into the intra-peritonea of 24 h water-deprived rats significantly and dose dependently increased the amount of water intake (Fig. 5, 6).

Water deprived rats showed no changes in water intake after injection of PCP (1, 5 and 10 mg kg^{-1}) (Fig. 7).

Figure 8 shows the cumulative food consumption after IP injection of most effective dose of Methyl and Methoxy derivatives. One way-ANOVA demonstrated that injection of Methyl and Methoxy derivatives (5 g kg^{-1}) increase food intake in comparison with saline and PCP (1-12 h post injection).

Figure 9 shows the cumulative water intake after injection of most effective dose of Methyl and Methoxy

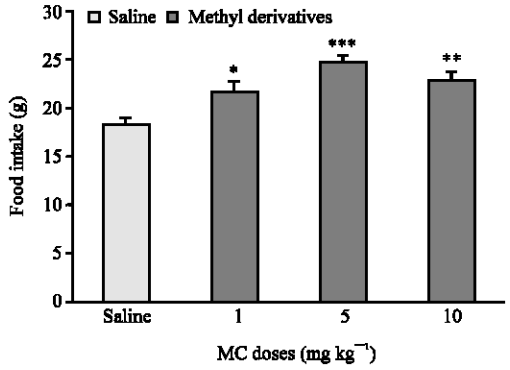

Fig. 2: Effects of IP injection of methyl derivatives (1, 5 and 10 mg kg^{-1}; 0.2 mL) or saline (0.2 mL) on food intake (12 h post-injection) in 24 h food deprived rats. Data expressed as the Mean±SEM (n = 6).*$p<0.05$, **$p<0.01$ and ***$p<0.001$ compared with saline-injected group

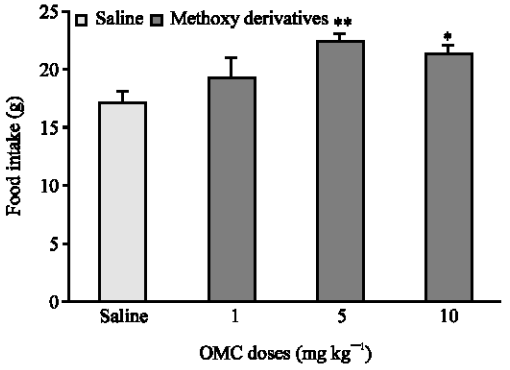

Fig. 3: Effects of IP injection of methoxy derivatives (1, 5 and 10 mg kg^{-1}; 0.2 mL) or saline (0.2 mL) on food intake (12 h post-injection) in 24 h food deprived rats. Data expressed as the Mean±SEM (n = 6).*$p<0.05$, **$p<0.01$

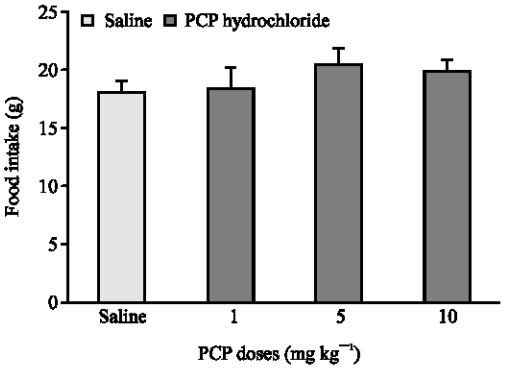

Fig. 4: Effects of IP injection of PCP hydrochloride (1, 5 and 10 mg kg^{-1}; 0.2 mL) or saline (0.2 mL) on food intake (12 h post-injection) in 24 h food deprived rats. Data expressed as the Mean±SEM (n = 6)

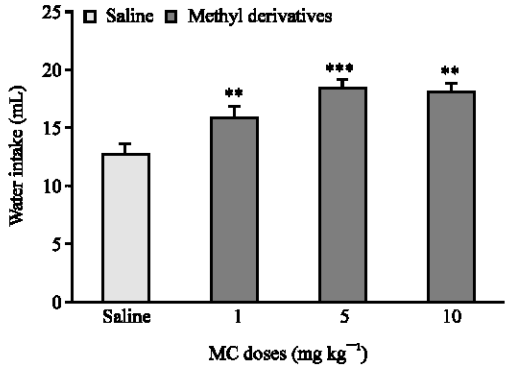

Fig. 5: Effects of IP injection of methyl derivatives (1, 5 and 10 mg kg^{-1}; 0.2 mL) on water intake (180 min post-injection) in 24 h water deprived rats. Data expressed as the Mean±SEM (n = 6). *p<0.05, **p<0.01 and ***p<0.001

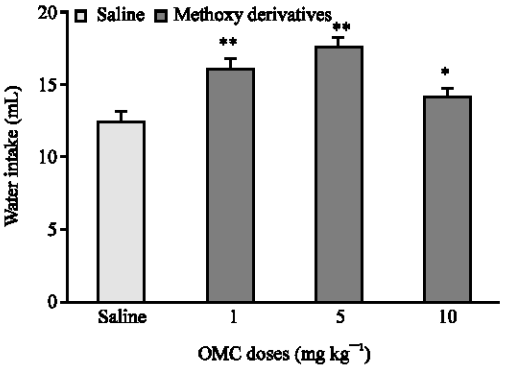

Fig. 6: Effects of IP injection of methoxy derivatives (1, 5 and 10 mg kg^{-1}; 0.2 mL) on water intake (180 min post-injection) in 24 h water deprived rats, Data expressed as the Mean±SEM (n = 6). *p<0.05 and **p<0.01

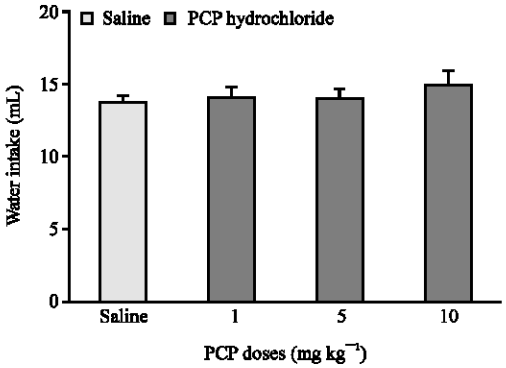

Fig. 7: Effects of IP injection of PCP hydrochloride (1, 5 and 10 mg kg^{-1}; 0.2 mL) on water intake (180 min post-injection) in 24 h water deprived rats, Data expressed as the Mean±SEM (n = 6)

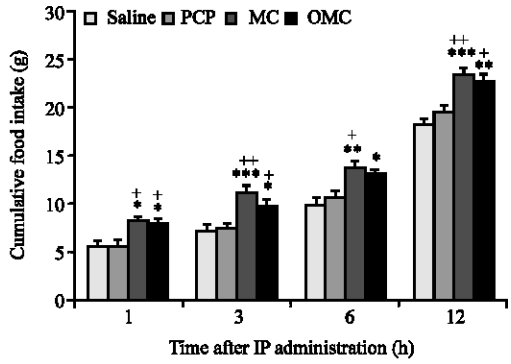

Fig. 8: Effects of IP injection of PCP (I), methyl derivatives (II) and methoxy derivatives (III) or saline (5 mg kg^{-1}; 2 mL) on cumulative food intake (1-12 h post-injection) in 24-h food-deprived rats. Data for food intake are expressed as the Mean±SEM (n = 6). *p<0.05, **p<0.01 and ***p<0.001 compared with saline-injected rats; +p<0.05 and ++p<0.01 compared with PCP

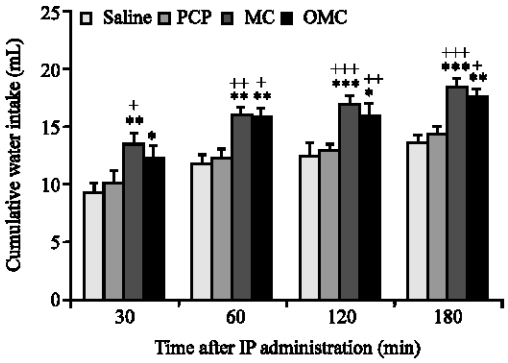

Fig. 9: Effects of IP injection of PCP (I), methyl derivatives (II) and methoxy derivatives (III) or saline (5 mg kg^{-1}; 2 mL) on cumulative water intake (30-180 min post-injection) in 24 h water-deprived rats. Data expressed as the Mean±SEM (n = 6). *p<0.05, **p<0.01 and ***p<0.001 compared with saline-injected rats; +p<0.05 and ++p<0.01 compared with PCP

derivatives. One way-ANOVA revealed that IP injection of Methyl and Methoxy derivatives (5 g kg^{-1}) increase water intake in comparison with saline and PCP (30-18 min. post injection).

DISCUSSION

Results of present study shows that methyl (II) and methoxy (III) hydroxyl derivatives of Phencyclidine (45), [(1-[1-(4-methylphenyl) (cyclohexyl, II)] 4-piperidinol II)

and (1-[1-(4-methoxyphenyl) (cyclohexyl)] 4-piperidinol, III)], increase food and water intake in wistar rats. As it mentioned before, PCP works primarily as an NMDA receptor antagonist, which blocks the activity of the NMDA receptor (Honey *et al*., 1985; Olney *et al*., 1991). Studies have shown that NMDA glutamatergic system has a role on modulation of feeding behaviors. Glutamate injections dose dependently induced decreases in food intake and feeding duration (Da Silva *et al*. 2006; Xu and Johnson, 1998; Zeni *et al*., 2000). In support of present results earlier studies showed that glutamatergic receptors antagonists increase food and water intake (Da Silva *et al*., 2006; Xu and Johnson, 1998; Zeni *et al*., 2000). Systemic injection of the non-competitive NMDA antagonist, MK801, increased food intake in rats (Burns and Ritter, 1997). Cholinergic systems may also have a role in modulation behavioral effects of PCP derivatives and would be caused to increase food and water intake by inhibition of nicotinic acetylcholine receptor channels (nAChR). Another studies also demonstrated that nicotine administration and activation of nAChRs associated with decreased in food and water intake and lower body weight in rats.

The PCP derivatives can also affect food and water intake by interaction with serotonergic system so that PCP administration increase brain serotonine level and affect different 5-HT receptors (Nabeshima *et al*., 1984; Svensson *et al*., 1995). Several studies have been shown the effects of serotonergic system and 5-HT receptors on control of food and water intake (Castro *et al*., 2002; Halford and Blundell, 1996; Saadoun and Cabrera, 2002).

So, it clears from the mentioned above that, different brain systems and receptors are involved in modulates behavioral effects of PCP and its analogues. Since, for PCP, there was not any increasing report for food and water intake (Balster and Chait, 1976), we applied two derivatives of this molecule with the changes in substitution on its phenyl and piperidine rings (II, III, scheme 1) that had more hydrophilic, polarity, electron distribution and dipole moments properties (Ahmadi *et al*., 2009) for increasing in feeding behavior.

Therefore, it seems that strong electron donating properties of the methyl group on para position of phenyl ring and also hydrophilic and polarity properties of hydroxyl group on the piperidine ring of the molecule (II) facilitate increases affinity to receptors and it is anticipated that food and water intake could be increased in comparison with PCP and vehicle (control). Also strong electron donating properties of the methoxy group on para position of phenyl ring and hydrophilic and polarity properties of hydroxyl group on the piperidine ring of the molecule (III) increased feeding consuming in comparison to the PCP and vehicle (control) but because of undesired reactions with cationoid intermediates (Ingold, 1969), little decrease in receptor binding could be anticipated. This increase is little than II but still it is higher than PCP and vehicle (control).

This study showed that both of two derivatives of phencyclidine, methyl (II) and methoxy (III) were more effective than PCP in modulation of ingestive behavior in rats and appropriate substitution of the methyl, methoxy and hydroxyl groups may result in ligands with higher affinity for the PCP site on receptors.

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